Italian Journal of Dermatology and Venereology 2024 May 10
DOI: 10.23736/S2784-8671.24.07666-7

GUIDELINES

Italian S3-Guideline on the treatment of atopic eczema Part 2: non-systemic treatments and treatment recommendations for special AE patient populations, adapted from EuroGuiDerm by the Italian Society of Dermatology and STD (SIDEMAST), the Italian Association of Hospital Dermatologists (ADOI) and the Italian Society of Allergological and Occupational Dermatology (SIDAPA)

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"Italian S3-Guideline on the treatment of atopic eczema– Part 2: non-systemic treatments and treatment recommendations for special AE patient populations, adapted from EuroGuiDerm by the Italian Society of Dermatology and STD (SIDEMAST), the Italian Association of Hospital Dermatologists (ADOI) and the Italian Society of Allergological and Occupational Dermatology (SIDAPA)" is a derivative of "European guideline (EuroGuiDerm) on atopic eczema: part II: non-systemic treatments and treatment recommendations for special AE patient populations. J Eur Acad Dermatol Venereol 2022 Nov;36(11):1904-1926. doi: 10.1111/jdv.18429. The original EuroGuiDerm guideline are available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jdv.18429.

ABSTRACT

SIDeMaST (Società Italiana di Dermatologia Medica, Chirurgica, Estetica e delle Malattie Sessualmente Trasmesse) contributed to the development of the present guideline on the systemic treatment of chronic plaque psoriasis. With the permission of EuroGuiDerm, SIDeMaST adapted the guideline to the Italian healthcare context to supply a reliable and affordable tool to Italian physicians who take care of patients affected by atopic dermatitis. The evidence- and consensus-based guideline on atopic eczema was developed in accordance with the EuroGuiDerm Guideline and Consensus Statement Development Manual. Four consensus conferences were held between December 2020 and July 2021. Twenty-nine experts (including clinicians and patient representatives) from 12 European countries participated. This second part of the guideline includes recommendations and detailed information on basic therapy with emollients and moisturizers, topical anti-inflammatory treatment, antimicrobial and antipruritic treatment and UV phototherapy. Furthermore, this part of the guideline covers techniques for avoiding provocation factors, as well as dietary interventions, immunotherapy, complementary medicine and educational interventions for patients with atopic eczema and deals with occupational and psychodermatological aspects of the disease. It also contains guidance on treatment for pediatric and adolescent patients and pregnant or breastfeeding women, as well as considerations for patients who want to have a child. A chapter on the patient perspective is also provided. The first part of the guideline, published separately, contains recommendations and guidance on systemic treatment with conventional immunosuppressive drugs, biologics and janus kinase (JAK) inhibitors, as well as information on the scope and purpose of the guideline, and a section on guideline methodology.

(*Cite this article as:* Argenziano G, Cusano F, Corazza M, Amato S, Amerio P, Naldi L, *et al*. Italian S3-Guideline on the treatment of atopic eczema. Part 2: non-systemic treatments and treatment recommendations for special AE patient populations, adapted from EuroGuiDerm by the Italian Society of Dermatology and STD (SIDEMAST), the Italian Association of Hospital Dermatologists (ADOI) and the Italian Society of Allergological and Oc-cupational Dermatology (SIDAPA). Ital J Dermatol Venereol 2024 May 10. DOI: 10.23736/S2784-8671.24.07666-7)

KEY WORDS: Eczema; Guideline; Consensus.

Overview of recommendations

General recommendations for systemic drugs in special atopic eczema patient populations and for topical drugs for treatment of atopic eczema[1] are given in Table I and Table II, respectively.

TABLE I.—*General recommendations for systemic drugs in special AE patient populations (for details see corresponding chapter).*

	Conventional systemic treatments			Biologics		JAK inhibitors		Rescue therapy
	Cyclosporin	Methotrexate	Azathiopirine	Dupilumab	Tralokinumab	Baricitinib	Upadacitinib	Systemic corticosteroids
Children and adolescents with AE who are candidates for systemic treatment	↑↑	↑	↑	↑↑			↑↑	
Dose for children	Licensed for ≥16 years Commonly used dosage in children: 2.5-5 mg/kg per day in two single doses	Off-label Commonly used dosage in children: 0.3-0.4 mg/kg per week	Off-label Commonly used dosage in children: 1-3 mg/kg per day	Licensed for ≥6 years Age 6-11: from 15 kg <60 kg, initially 300 mg s.c. day 1 and 15 followed by 300 mg Q2W Age 12-17: <60 kg: initially 400 mg s.c. day 1 followed by 200 mg Q2W, when ≥60 kg: initially 600 mg s.c. day 1 followed by 300 mg Q2W	Off-label	Off-label	Licensed for ≥12 years Age 12-17 (≥30 kg BW); 15 mg per day	General unspecific license for children for stroid responsive skin disease Max dosage: 1 mg/kg per day
Pregnancy (in candidates for systemic treatment)	↑	↓↓	↑	0		↓↓	↓↓	↑ Prednisolone (0.5 mg/kg/d) *only* as rescue therapy for acute flares
Breastfeeding	↓	↓	↓	0		↓	↓	↑ Prednisolone (0.5 mg/kg/d) *only* as rescue therapy for acute flares

[1]SmPC; Q2W: once every 2 weeks.

Symbols	Implications (adapted from GRADE)[2]
↑↑	We believe that all or almost all informed people would make this choice
↑	We believe that most informed people would make this choice, but a substantial number would not
0	We cannot make a recommendation
↓	We believe that most informed people would make a choice against this intervention, but a substantial number would not
↓↓	We believe that all or almost all informed people would make a choice against this intervention
	No recommendation

TABLE II.—*General recommendations for topical drugs for the treatment of atopic eczema (for details see corresponding chapter).*

Overall recommendation	TCS ↑↑		TCI ↑↑	
	TCS class I and II	TCS class III and IV	Tacrolimus 0.1% Tacrolimus 0.03%	Pimecrolimus 1%
For further information see background text	Class I not suitable for long-term proactive treatment Long-term proactive treatment only class II	Acute flare Proactive treatment with TCS class III Class IV not for long-term daily treatment or head and neck Class IV not recommended for proactive treatment either	Acute flare Long-term proactive treatment Especially in face, intertriginous site, anogenital area	Acute flare Especially in face, intertriginous site, anogenital area
Most important side effects	Skin atrophy Telangiectasia Striae distensae Ecchymosis Hypertrichosis Perioral dermatitis	Skin atrophy Telangiectasia Striae distensae Ecchymosis Hypertrichosis Perioral dermatitis Corticosteroid addiction syndrome Suppression of adrenal function	Initial warmth, tingling or burning	Initial warmth, tingling or burning
	TIC class II and III are off-label for proactive treatment		In label for proactive treatment	Not suitable for proactive treatment
Special considerations				
Suitable for **children >2 to <16 years** of age	Yes	Yes	Yes (0.03%)[2]	Yes[2]
Suitable for **babies <2 years** of age	Yes	Under specialist supervision	Yes (0.03%)[1]	Yes[2] (from the age of three months)
Suitable during **pregnancy**	Yes	Yes	Yes (0.03% and 0.1%)[1]	Yes[1]
Suitable during breastfeeding	Yes	Yes	Yes (0.03% and 0.1%)[1]	Yes[1]
Suitable for pruritus	Yes	Yes	Yes (0.03% and 0.1%)	Yes

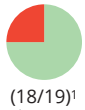
[1]Off-label use; [2]licensed use.

Symbols	Implications (adapted from GRADE)[2]
↑↑	We believe that all or almost all informed people would make this choice
↑	We believe that most informed people would make this choice, but a substantial number would not
0	We cannot make a recommendation
↓	We believe that most informed people would make a choice against this intervention, but a substantial number would not
↓↓	We believe that all or almost all informed people would make a choice against this intervention
	No recommendation

Patients' perspective

We recommend that health care providers treat each patient as a whole person, not just the skin, while considering the burden of skin disease on life.	↑↑	100% Patient/caregiver consensus
We recommend that health care providers use the principle of shared decision making, *i.e.* discuss the patient's beliefs, lifestyle and preferences when deciding on a treatment plan.	↑↑	100% Patient/caregiver consensus
We recommend that patients with comorbidities are treated by multidisciplinary teams.	↑↑	100% Patient/caregiver consensus
We recommend that health care providers are given time, training and resources to educate patients/caregivers in lay language about treating and managing their own condition.	↑↑	100% agreement Patient/caregiver consensus
We recommend that patients/caregivers receive adequate knowledge, skills, resources and support to treat their AE at home and cope with its impact on life.	↑↑	100% agreement Patient/caregiver consensus
We recommend that patients have access to all available treatments and that these treatments are affordable and practical.	↑↑	100% agreement Patient/caregiver consensus

Basic emollients and moisturizers

We recommend gentle cleansing and bathing procedures especially in acutely inflamed or superinfected skin in patients with AE.	↑↑	100% agreement  Patient/caregiver consensus
We recommend gentle cleansing and bathing procedures especially in acutely inflamed or superinfected skin in patients with AE.	↑	>75%  (17/19) Expert consensus
We suggest against the use of alkaline soaps in patients with AE.	↓	100% agreement  (19/19) Expert consensus
We suggest that patients with AE use body care products, for example gentle cleansers that do not contain potent irritants or relevant allergens.	↑	
We recommend daily use of emollients, liberally and frequently for patients with AE, as basic treatment of the disturbed skin barrier function.	↑↑	>75%  (20/23) Expert consensus
We recommend using moisturizers with a hydrophilic formula in the summer and moisturizers with a high lipid content in the winter in patients with AE.	↑	>75%  (15/18)[1] Expert consensus
We recommend to apply emollients immediately after bathing or showering and soft pat drying ("soak and seal technique").	↑↑	100%  (19/19) Expert consensus
We recommend the use of emollients as background treatment to prevent flares and to reduce the symptoms of AE.	↑↑	>75%  (18/19)[1] Expert consensus

[1]One abstention.

[1]One abstention.

Emollient therapy

Basic emollient therapy

Basic emollient therapy is the essence of every treatment of AE.[3, 4] Emollients usually contain a humectant or moisturizer (promoting stratum corneum hydration) such as urea or glycerol and an occludent (reducing evaporation such as lipids or petrolatum). Recently, marketing of non-medicated 'emollients' containing active ingredients has blurred the line between pure emollients working through their physical properties and topical drugs.

Throughout this guideline, 'emollients' are defined as 'topical formulations with vehicle-type substances without active ingredients', whereas 'emollients plus' refers to '*topical formulations with vehicle-type substances plus additional active, non-medicated substances.*'[5]

A Cochrane review compared emollients containing moisturizers *versus* no moisturizer and found that the former were better at reducing investigator-reported severity and led to fewer flares and a reduction in the use of corticosteroids.[6] There have also been studies that have examined the use of glycerol-containing moisturizers *versus* vehicle or placebo.[3, 7] More participants in the glycerol group noticed skin improvement but the MID (minimal important difference) was not met.[8]

Some studies have investigated oil-containing emollients *versus* no treatment or vehicle and found no significant differences between the groups. In one study, there were fewer flares in the oil group and reduced use of topical corticosteroids. Overall, topical active treatment combined with emollients was more effective than emollient treatment alone with various outcomes measured.[6, 9]

It is recommended to apply emollients immediately after bathing or showering and soft pat drying. A small study suggests that an emollient applied alone without bathing may have a longer duration as measured by capacitance.[10] Only emollient preparations free of protein allergens or haptens known to cause contact allergy (such as lanolin/wool wax alcohol or preservatives such as methylisothiazolinone)[11] should be used, especially in children under the age of 2. The long-term use of maintenance (*e.g.* twice weekly) emollient therapy after remission may prolong the duration of flare-free intervals.[9, 12, 13]

The direct, sole use of emollients on inflamed skin is often poorly tolerated, and it is better to treat the acute flare first with anti-inflammatory procedures including wet wraps (see chapter anti-inflammatory treatment). Emollients are the mainstay of management. Hydration of the skin is usually maintained by at least twice daily applica-

tion of emollients with a hydrophilic base containing for instance 5% urea or glycerol.[14]

Galenic aspects of the formula should be considered with regard to seasonal differences (more hydrophilic in summer, more lipid content preferably in winter). Also, regional aspects of body sites involved play a role (pastes for intertriginous areas, not too greasy for the face).

Depending on the acuity of the skin condition, lipophilic bases may also be helpful, especially in more chronic conditions.

The use of barrier ointments, bath oils, shower gels, emulsions or micellar solutions that enhance the barrier effect is also recommended.

The amount of the topical that is applied is crucial; about 250 g/week are recommended.[5, 15] It may follow the fingertip unit rule: a fingertip unit (FTU) is the amount of ointment expressed from a tube with a 5 mm diameter nozzle and measured from the distal skin crease to the tip of the index finger (*ca*. 0.5 g); this is an adequate amount for application to two adult palm areas, which is approximately 2% of an adult body surface area.[16]

The cost of quality emollient (low in contact allergens or hazardous substances) therapies often restricts their use because such therapies are considered to be non-prescription drugs (except for pediatric patients in some European countries).[17]

The use of pure oil products such as coconut or olive oil instead of emulsions will dry out the skin and increase transepidermal water loss and thus is not recommended.

Emollients with non-medicated, active ingredients (emollients plus)

Several non-medicated products for topical treatment of AE contain putative active ingredients but neither fulfill the definition of, nor need a license as, a topical drug. These products, referred to as 'emollients plus' by the European guideline since 2018, may contain, for example, flavonoids such as licochalcone A, saponins and riboflavins from protein-free oat plantlet extracts,[12] bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis* species,[18-20] or a synthetic derivative of menthol such as menthoxypropanediol.[5]

Oral supplementation with unsaturated fatty acids, such as gammalinolenic acid from evening primrose oil or eicosapentaenoic acid from fish oils, has been studied as a way to improve barrier function and enhance patient acceptance, but has shown conflicting results.[21] The efficacy of topical evening primerose oil-containing emollients depends on the choice of vehicle.[22]

To improve the moisturizing effect of the emollient, several ingredients are used such as urea or glycerol or propylene glycol. Emollients can also be enriched by other ingredients such as moisturizers or tannin, ammonium bituminosulfonate, flavonoids or unsaturated fatty acids such as omega-3 or omega-6 compounds.

Prevention aspect

Emollients have a definite place in secondary and tertiary prevention in patients with AE. There is controversial evidence on primary preventive effects of emollients: newborns with high risk of atopy/AE who were treated daily with emollients developed less atopic dermatitis or allergic sensitisations in the first year of life.[23, 24] Two larger and longer randomized controlled trials with a less stringent intervention did not confirm these effects.[25, 26] Some experienced clinicians still feel comfortable using emollients in individuals at risk of AE early in life.

Cleansing and bathing

Skin hygiene procedures play an important role in the management of AE, especially in infants and young children. Some authors consider alkaline soaps as disadvantageous compared with liquid cleansers with adequate skin surface pH and lipid content.[27] Bathing is regarded as generally superior to washing or showering – especially in young children - also with regard to emotional and psychological interactions between infants and parents.[28, 29] The water temperature should not be too high.[30] A recent systematic review has shown that daily bathing or showering is not associated with changes in disease severity, but three studies with qualitative analysis found an improvement of itch and IGA by bathing. Showering may be permitted.[31]

The skin must be cleansed thoroughly, but gently and carefully, to get rid of crusts and mechanically eliminate bacterial contaminants in case of superinfection. Cleansers with or without antiseptics can be used. The duration of action of antiseptics is rather short, and mechanical cleansing is probably more important. Cleansing agents are available in various galenic forms (syndets, aqueous solutions) and should not be too irritating and should not contain strong allergens.[11, 32] The pH values should be between 5 and 6. A small randomized study regarding the frequency of bathing procedures did not show any difference between twice weekly *versus* every day.[33]

In infants, it is easier to perform the first stage of gentle cleansing on the nappy mattress rather than directly in the bathtub. The mechanical component of cleaning helps to remove bacteria from the stratum corneum. Further

cleansing is followed by a rapid rinse performed in the bath (27–30°C). The short duration of the bath (approx. 5 min) and the use of bath oils (added for the last 2 min of bathing) are aimed at avoiding epidermal dehydration. Topical emollients are preferentially applied directly after a bath or a shower following gentle drying when the skin is still slightly moist.[10] It should be emphasized that most bath oils commercially available in Europe are practically free of proteinaceous allergens.[34] A recent study found no evidence for a benefit of adding bath additives to standard treatment regimens,[35] while another study found that some bathing additives such as dead sea salt, oatmeal or natural oils, may augment the benefit and reduce the need for or side-effects of pharmacological treatments.[36]

The addition of antiseptics such as sodium hypochlorite (bleach bath) has proved helpful and is discussed in the chapter 'antimicrobial therapy'.

Adding sodium chloride to bathing water containing oil has been recommended because of its keratolytic and skin moisturizing effect in concentrations up to 5%.[37] In adults, higher salt concentrations with the addition of magnesium have been used to mimic the effect of balneotherapy in the dead sea, also together with UV phototherapy[38] (see chapter phototherapy).

Preventative and maintenance treatments for atopic dermatitis (AD) in Italy

All basic non-medicated emollients, emollients with active ingredients (emollients plus) and cleansing agents with or without antiseptics can be freely bought by patients. However, full or partial reimbursements are not provided by the Italian NHS (Servizio Sanitario Nazionale, SSN) to any patient regardless of age, annual income and severity of the disease.

Anti-inflammatory treatment

We recommend the use of topical corticosteroids (TCS) as anti-inflammatory agents. **We recommend** the use of topical calcineurin inhibitors (TCI) as anti-inflammatory agents.	↑↑	>75%  (24/26) Expert consensus
We recommend using anti-inflammatory topical agents according to the fingertip unit role.	↑	>75%  (23/26) Expert consensus
We recommend the use of wet wraps with diluted (see background text) or low potency topical corticosteroid in acute AE.	↑	>50%  (14/22) Expert consensus
We recommend TCS in AE especially for treatment of acute flares. **We recommend** to note and adequately address patients' concerns or fears about corticosteroid side effects. **We recommend** using TCI particularly in skin areas with a risk of skin atrophy due to TCS application (face, intertriginous sites, anogenital area).	↑↑	100% agreement  (23/23) Expert consensus
We suggest initial treatment with topical corticosteroids before switching to a TCI to reduce the risk of skin stinging and burning.	↑	100% agreement  (23/23) Expert consensus
We recommend proactive therapy (*e.g.* twice weekly application) with a suitable TCS or a suitable TCI (see background text) to reduce the risk of relapse and for better disease control.	↑↑	100% agreement  (22/22) Expert consensus

Effective topical therapy depends on three fundamental principles: sufficient potency, sufficient dosage and correct application.[39] Current approved topical anti-inflammatory therapies are corticosteroids (TCS), calcineurin inhibitors (TCI) and a phosphodiesterase 4 (PDE-4) inhibitor, which is approved in the European Union but not yet available.

The amount of anti-inflammatory topicals applied should follow the fingertip unit rule (see chapter emollient therapy). Topical treatment should ideally be applied on hydrated skin, especially when using ointments ('soak and seal' approach).

Topical anti-inflammatory therapy can be done by two approaches: reactive and proactive management. In the reactive treatment regimen, anti-inflammatory topical therapy is applied to lesional skin only and is stopped or rapidly tapered once visible lesions are cleared or almost cleared. Proactive therapy is defined as a combination of predefined, long-term, anti-inflammatory treatment applied usually twice a week to previously affected areas of skin in combination with liberal daily use of emollients on the entire body. Additionally, it is marked by a predefined appointment schedule for clinical examinations.[40] The proac-

tive regimen is started after the therapy of the acute flare, when lesions have been successfully treated with regular anti-inflammatory therapy. The duration of proactive management is usually adapted to the severity and persistence of the disease.[41]

Patients with acute, erosive and oozing lesions, as well as pediatric patients, sometimes do not tolerate standard topical application and may first be treated with 'wet wraps' until the oozing stops. Where clinically superinfected skin is suspected, adding oral antibiotic cover should be considered. Wet wrap medications are highly effective in acute AE and improve tolerance of emollient application. Wet wrap dressings with diluted or lower potency corticosteroids (group II, III, typical dilutions used are 1:3-1:10, usually just for a few days is sufficient) are a safe crisis intervention treatment of severe and/or refractory flares of AE with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effects.[42-45] Wet wraps can be conducted with topical corticosteroid creams and ointments.[46] However, this treatment approach is not standardized yet, and the evidence that it is more effective than conventional treatment with topical corticosteroids in AE is not of high quality. Simple or occlusive medications in less sensitive skin areas and for brief time periods may also increase efficacy and speed up lesion resolution.

Topical corticosteroids

Mechanisms of action and efficacy

Topical corticosteroids (TCS) are a first-line anti-inflammatory treatment, typically applied on acutely inflamed skin according to patient needs (pruritus, sleeplessness and new flare).[47, 48] The lipophilicity and the low-molecular weight of TCS allow good penetration into the skin and binding to a steroid receptor in the cytoplasm. The CS-receptor complex acts as a transcription factor with dual activity, decreasing the synthesis of proinflammatory cytokines and increasing the synthesis of anti-inflammatory mediators.

The potency of topical corticosteroids is grouped according to Niedner from mild (class I) to super-potent (class IV).[49] This classification is used across Europe and throughout this guideline, except for France, where this classification is similar but in an inversed ranking. The classification used in the US is even different, and recognizes seven groups: from VII (weakest) to I (most potent).

Latest generation TCS with a better risk–benefit ratio are favored over earlier generation TCS.

Dosage: acute flare, short term and long term

When choosing a TCS, in addition to potency the galenic formulation, patient age and body area to which the medication will be applied should be considered. In children, low-to-moderate potency TCS should be used routinely. Adolescent and adult patients can use potent to very potent TCS under specialist supervision in an acute flare of AE for a short period of time. Potent and very potent TCS are sometimes also used in younger age groups under specialist supervision.

Treatment of the face and especially the peri-orbital region or other sensitive areas (folds and neck) should be restricted to mild-to-moderate TCS (class I and II).[50]

With mild disease activity, a small amount of TCS twice to three times weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults, roughly adapted to affected body surface area), associated with a liberal use of daily emollients allows for a good weekly maintenance treatment routine.

Also, patients with moderate or severe AE can benefit from long-term proactive treatment with a moderate to potent TCS. Twice weekly application of fluticasone proprionate or methylprednisolone aceponate (TCS class III) has shown a significant reduction in AE-flare recurrence. Outside of the context of clinical trials, similar experience also exists for other class III and even class II TCS.[47, 48, 51]

Safety

For further details on the well-established safety considerations of TCS, see the full version of the guideline.

Monitoring

Monitoring by physical examination for cutaneous side-effects during long-term use of potent TCS is very important.

Itch, which can be assessed by itch Numeric Rating Scale (NRS), is the key symptom for evaluating the response to treatment, and tapering should not be initiated before the itch has largely resolved. In addition to continuous background emollient skin care, one to two applications of TCS per day may be necessary with low- and mid-potency TCS to reduce the itch at the beginning, but one correctly dosed treatment per day is typically sufficient.[52, 53] Dose tapering is usually performed to avoid rebound flares, although no controlled studies have demonstrated its usefulness. Tapering strategies consist of switching to a less potent corticosteroid or keeping a more potent one while reducing the frequency of application (intermittent regimen).

The most constructive way to spare corticosteroids and avoid corticosteroid-related side-effects is to start the anti-inflammatory treatment early and use them intensively during the acute flares.[39]

Combination with other treatments

The combination of TCS with topical calcineurin inhibitors (TCI) at the same site does not seem to be useful. At least in pediatric patients with severe AE, the efficacy and safety profile of pimecrolimus cream 1% combined with fluticasone were similar to that of fluticasone alone.[54] Treating sensitive body areas such as the face (with predilection to skin thinning) with TCI while treating other affected body areas with a TCS is a common practice but class I and II TCS can be used equally effectively on the face and neck for acute flares. Initial treatment with TCS may be considered in patients with acute flare to minimize TCI site reactions (stinging and burning).[41]

Special considerations

Patient fear of side-effects of corticosteroids (corticophobia) is quite common and should be recognized (*e.g*. by TOPICOP score)[55] and adequately addressed to improve adherence and avoid undertreatment.[56-58] In pregnancy and lactation, lower potency TCS should be used where possible (see chapter pregnancy, breastfeeding and family planning).

Topical corticosteroids in Italy

All topical corticosteroids' formulations are fully reimbursed by the SSN (class of reimbursement A) for the treatment of AD provided that a specific certification (note 88) is issued by a specialist of the SSN (https://www.aifa.gov.it/nota-88). Products with corticosteroids combined with other active principles, *e.g*. salicylic acid, antiseptic agents and antibiotics, are never reimbursed.

Topical calcineurin inhibitors

Mechanisms of action and efficacy

Two topical calcineurin inhibitors (TCI) (tacrolimus ointment and pimecrolimus cream) are licensed for AE treatment. Pimecrolimus 1% cream and tacrolimus 0.03% ointment are approved in the EU from 2 years of age and above. Elidel® cream has additionally been approved in Europe down to 3 months of age. Tacrolimus 0.1% ointment is only licensed in patients age 16 years and above. TCI have an immunosuppressive effect by inhibiting the activity of the phosphorylase enzyme calcineurin and thus inhibiting the activation of T lymphocytes. The transepidermal penetration of TCI is lower than that of TCS.[59, 60] TCI are a first-line therapy for sensitive areas where TCS use is likely associated with side-effects or in areas where TCS has already caused side-effects. The efficacy of both formulations has been demonstrated against vehicle in clinical trials for short-term (3 weeks)[61, 62] and long-term use up to 1 year.[63, 64]

The efficacy of long-term monotherapy with tacrolimus ointment has been demonstrated in children and adults.[65-67] In adults, long-term proactive treatment with 0.1% tacrolimus ointment has shown good effectiveness for flare prevention, similar to class III TCS.[66] Proactive tacrolimus ointment, but not pimecrolimus 1% cream, has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving quality of life (QoL) in both adults and children.[68, 69] Pimecrolimus 1% cream has been studied in infants and children in a combination regimen with TCS,[70, 71] the latter being given if a flare occurred. Fewer data are available for children under 2 years of age.[72, 73] In children, twice-weekly treatment with tacrolimus 0.03% ointment has been reported to reduce the number of flares and to prolong flare free intervals.

Dosage: acute flare, short term and long term

The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to that of a potent corticosteroid (class III),[65, 66, 74] and 0.1% tacrolimus ointment is clearly more effective than 1% pimecrolimus cream.[67]

TCS and TCI can be used in a daily regimen during an acute AE flare. The efficacy of intermittent treatment twice or three times weekly has been investigated in different trials.[68, 69]

Safety

Safety data of both TCI have been reported in many clinical trials and registries, and high-quality long-term safety data have been published from 10-year tacrolimus and 5-year pimecrolimus studies, demonstrating the safety of this anti-inflammatory treatment in daily practice.[75, 76]

None of the TCI induce skin atrophy.[77, 78] This favors their use over TCS in sensitive body areas such as the eyelid region, the perioral skin, the genital area, the axilla region or the inguinal fold, and makes them suitable for long-term management. In addition, the use of TCI may

potentially reverse some of the side-effects of TCS when applied on sensitive areas.[79]

After initial concerns from animal studies, resulting in a black box warning from the USA Food and Drug Administration (FDA), no convincing evidence for an increased risk of lymphoma has been found in humans.[80] A long-term safety study over 10 years using tacrolimus ointment 0.03% or 0.1% in children did not show an increased risk of cancer or lymphoma.[81] The application of TCI is not associated with an increased risk of non-melanoma skin cancer, other malignancies or photocarcinogenicity.[76, 82-86] In a retrospective cohort study with more than 90,000 participants and over 10 years follow-up, no increased risk of basal cell carcinoma or squamous cell carcinoma was observed.[87] The JOELLE study investigated the risk of lymphoma and skin cancers with the use of TCI and TCS in a very large cohort of pediatric and adult patients and found a positive association. However, given the study design, confounding factors, such as disease severity, have not been ruled out.[88] A recent pediatric prospective observational cohort study (APPLES, N.=7954) found no significant association between regular tacrolimus use and lymphoma risk over a 10-year follow-up period. Nevertheless, given that the long-term oral use of ciclosporin (calcineurin inhibitor) is associated with an increased photocarcinogenicity risk in solid organ transplant patients, exposure of the skin to sunlight should be minimized and effective UV protection through the use of sunscreens and appropriate clothing should be recommended in all patients using TCI. Furthermore, the combined use of TCI and phototherapy should be avoided.[89]

Clinicians should be aware of the black-boxed warning on the use of TCI inhibitors and may discuss this with patients to improve adherence, even if observational studies have not found a convincing association between long-term TCI use and cancer development.[81]

Monitoring

Monitoring by physical examination for cutaneous side-effects during long-term treatment with TCS and TCI is important (also see above).

Special considerations

Although TCI are not approved in pregnancy and lactation (see chapter pregnancy, breastfeeding, family planning), off-label use in pregnancy and lactation is possible as there is no teratogenic potential reported for the entire substance class.[90]

Tacrolimus

In Italy, both tacrolimus 0.03% ointment and tacrolimus 0.1% ointment are approved for the treatment of moderate and severe AD in adults and adolescents (≥16-year-old) who have not responded adequately or who are intolerant to conventional therapies. Tacrolimus 0.03% is approved for children ≥2-year-old as well.
The drug is fully reimbursed (class A) with a prescription by a dermatologist, allergist or pediatrician of a SSN healthcare unit after filling out an authoritative standard plan form that is valid up to 6-12 months.
Both original product and generic products are available but only the cheapest generic product is fully reimbursed. (https://www.codifa.it/farmaci/c/carelimus-tacrolimus-monoidrato--immunosoppressori) Treatment should be discontinued if an improvement is not achieved after two weeks with daily applications. Tacrolimus is also approved for the prevention of exacerbation and for the extension of intervals free from exacerbation (pro-active treatment protocol) with two weekly applications in patients with very frequent exacerbations (*e.g.*, 4 or more times a year) who have shown an initial response to a treatment lasting up to six weeks with tacrolimus ointment twice a day (lesions disappeared, almost disappeared or present in a mild form). This maintenance regimen should be discontinued within 12 months.

Pimecrolimus

Pimecrolimus 1% cream is approved for the treatment of mild to moderate AD of patients ≥2 year old who are not responsive to topical corticosteroids or corticosteroids are contra-indicated.
Prescription modalities in Italy are the same as for topical tacrolimus.
https://www.codifa.it/farmaci/e/elidel-pimecrolimus-dermatologici

Topical phosphodiesterase 4 inhibitors

Mechanisms of action and efficacy

The topical phosphodiesterase 4 (PDE-4) inhibitor crisaborole is approved for treatment of mild-to-moderate AE in patients 2 years of age and older in the USA, Canada, Australia, Israel and Hong Kong. Crisaborole was approved in the European Union in 2020 but is not commercialized in the European market. Therefore, no recommendations are made.

Crisaborole

Crisaborole (Staquis©, Pfizer Europe, Bruxelles, Belgium) is approved in Italy to control the symptoms of mild to moderate AD in adults and children older than 2 years of age. The ointment should not be used on more than 40% of the body surface area. A registry for additional monitoring is provided but the drug is not currently available and reimbursed in Italy. (https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004849_048611_FI.pdf&retry=0&sys=m0b1l3)

Upcoming topical treatment

Upcoming topical therapies include several topical Janus Kinase (JAK) inhibitors. First, promising phase II clinical trial data with the topical JAK inhibitor tofacitinib have been published.[91] Despite these promising results, the clinical development program of tofacitinib has been stopped. Delgocitinib has been approved for use in AE in Japan.[91, 92] In a 4-week study, the selective JAK-1 and JAK-2 inhibitor ruxolitinib showed a similar or even higher efficacy in mild-to-moderate AE compared with triamcinolone cream (group III TCS) and has recently been approved in the United States.[93] Other JAK inhibitors with similar or different selectivity (brepocitinib) are in the pipeline for topical therapy, but none is currently licensed in Europe.

Antimicrobial treatment

We suggest treatment with topical antiseptic drugs — including sodium hypochlorite 0.005% baths — in patients with a history of recurrent skin infections.	↑	100% agreement (24/24) Expert consensus

Antibacterial treatment

We recommend a short course of systemic antibiotics only in AE patients with extensive clinically superinfected lesions.	↑↑	100% agreement (25/25) Expert consensus
We suggest against the long-term application of topical antibiotics, due to the risk of resistance development.	↓	
We suggest that topical anti-inflammatory treatments are continued during the treatment of Staphylococcus aureus superinfection episodes.	↑	

The prevalence of *Staphylococcus aureus* (SA) colonization among patients with AE is typically above 80% for lesional skin and 40% for non-lesional skin *versus* 10% in healthy individuals, but this depends largely on the culture methods used. The density of the colonization correlates with the disease severity.[94] Topical corticosteroids and calcineurin inhibitors reduce the colonization rate of SA in AE. Although AE patients are prone to SA skin infections, most AE patients colonized by SA do not show overt signs of infection (*i.e.* weeping, honey-colored crusts and pustules). Clinical signs of skin inflammation during AE flares may overlap with signs of skin infection, making the diagnosis of skin infection *per se* challenging.[95] Bacterial swabs are commonly unhelpful, as they do not alter the treatment approach, unless the patient is infected with a resistant bacterial species. SA is a major trigger of AE flares, but its role in the development of AE is still debated. There are a number of mechanisms through which SA can drive eczematous inflammation, including the release of superantigen toxins, which enhance T-cell activation of superantigen-specific and allergen-specific T cells, the expression of IgE antistaphylococcal antibodies and increased expression of IL-31 which leads to pruritus and subsequent scratching.[95, 96] Scratching favors binding of *SA* to the skin, and the increased amount of *S. aureus*-derived ceramidase aggravates the skin barrier defect. Moreover, superantigen production increases the expression of alternative glucocorticoid receptors that do not bind to topical corticosteroids, which leads to treatment resistance. Biofilm formation by AE-associated staphylococci most certainly also plays a major role in the occlusion of sweat ducts and leads to inflammation and pruritus.[97]

Antiviral treatment

We recommend treating eczema herpeticum without delay using systemic antiviral therapy, such as acyclovir.	↑↑	100% agreement (23/23) Expert consensus
We recommend performing vaccinations in line with national guidelines.		

Viral infections, including herpes simplex, varicella zoster, molluscum contagiosum, smallpox and coxsackie viruses, occur more frequently in AE patients than in healthy individuals, with a tendency to disseminated, widespread disease.[98]

Eczema herpeticum (EH), a disseminated herpes simplex virus (HSV) infection, is a potentially serious complication of AE that requires immediate medical action.

Patients, mostly children, present with disseminated vesicles, fever and lymphadenopathy and can develop complications such as keratoconjunctivitis, meningitis and encephalitis. Predisposing factors of first episode of EH or recurrent EH are early onset and severe or untreated forms of AE with high IgE levels and atopic comorbidities (extrinsic AE). Pretreatment with topical corticosteroids or calcineurin inhibitors is not associated with an increased risk of developing EH. There is no evidence to recommend discontinuation of topical anti-inflammatory treatments during an EH outbreak.[99] Mainstay of EH therapy is systemic treatment with aciclovir or valaciclovir.[100] Treatment should be started immediately once the clinical diagnosis is made.[5]

Varicella-zoster virus (VZV) infection in an immunocompetent child is usually a mild, self-limiting disease. This infection is, however, known to facilitate secondary local or systemic bacterial infection and is a particular concern in children with AE. Earlier studies demonstrated the safety and efficacy of VZV vaccination in these children, who appear to benefit from this vaccination.[101] Moreover, in children with AE, the immune response to VZV vac cine is comparable to that in healthy children.[102] Therefore, parents of atopic children should be encouraged to fully immunize their children depending on specific local guidelines.

Molluscum contagiosum virus (MCV) infection is in general benign and self-limiting but frequent in patients with severe AE.

A large variety of topical treatments have been reported such as cantharidin, potassium hydroxide, tretinoin cream and topical cidofovir.[103] Physical therapies, including cryotherapy and curettage, are also effective, but not always well tolerated in pediatric patients and usually unnecessary given the self-limiting nature of MCV infections.[104] Topical treatment of AE with TCS should be continued during MCV infection.

Eczema coxsackium (EC) is a disseminated form of coxsackie virus infection mostly occurring in children with active AE lesions.[105] The coxsackie virus A6 strain leads to atypical disease manifestations, which are classified as: 1) a diffuse form (lesions extended to the trunk); 2) an acral form (lesions with a mainly acral distribution); or 3) eczema coxsackium (disseminated lesions on preexisting eczematous areas).[106] This rash may be confused with bullous impetigo or eczema herpeticum. Symptomatic treatment includes topical corticosteroids and wet wrap therapy.[107, 108]

Regional vaccination programs should be followed by all AE patients as recommended. The denial of vaccination because of diagnosed AE is a misconception possibly leading to fatal consequences.

Antifungal treatment

We suggest topical or systemic anti-fungal therapy in some patients with AE, mainly in those suffering from the "head and neck" variant of AE and with demonstrated IgE sensitization to *Malassezia* spp.	↑	>95%  (23/24) Expert consensus

Despite its role as a commensal on healthy human skin, *Malassezia* spp. is attributed a pathogenic role in AE, as it may interact with the local skin immune response and barrier function. Through a deficient skin barrier, *Malassezia* spp. may activate keratinocytes and dendritic cells causing secretion of a range of proinflammatory cytokines including IL-4, IL-13 and IL-17.[109-111] The most common class of antifungal drugs prescribed for AE patients are azoles, such as ketoconazole and itraconazole, which also have some anti-inflammatory properties.[112] Due to a better benefit-to-side effect ratio, imidazole derivates (fluconazole or itraconazole) should be pre- scribed instead of ketoconazole for systemic treatment. In summary, antifungal treatment with either topical ketoconazole or ciclopiroxolamine or systemic itraconazole or fluconazole can be considered for those patients who suffer from head-neck dermatitis, particularly for those who are characterized by clear IgE- sensitization to *Malassezia* spp.

Systemic antibiotics, antivirals and antifungals

In Italy, all systemic antibiotics, antivirals and antifungals are fully reimbursed by the SSN if prescribed by a SSN practitioner or specialist. Topical antibiotics, antivirals and antifungals are never reimbursed by the SSN and patients have to pay out of the pocket.

Antipruritic treatment

Itch is the most important clinical symptom in AE with particular impact on emotional dimensions of perception as compared with other pruritic dermatoses. Most drugs successfully used in AE patients, because they are targeting the inflammation, will also have a measurable effect on the itch. Only a limited number of studies have specifically assessed the antipruritic effect of treatment modalities in AE. The management of itch in AE requires a multidimensional approach that treats itch itself but also the contributing factors, such as dry skin and skin inflammation.

Antipruritic effect of anti-inflammatory treatment

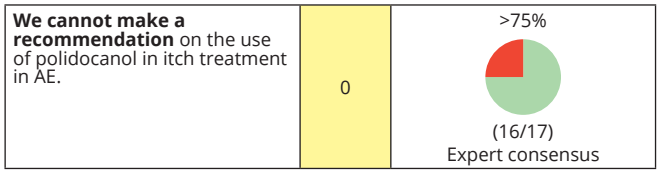
Anti-inflammatory agents, whether topical or systemic, reduce skin lesions and significantly relieve itch. Although topical corticosteroids do not act as direct antipruritic agents,[113] several studies have described the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others studied.[114]

Topical calcineurin inhibitors relieve pruritus significantly in AE. Itch is completely relieved after the first days of treatment in both adults and children. Topical calcineurin inhibitors appeared to significantly reduce AE itch by 36% compared with vehicle application.[114]

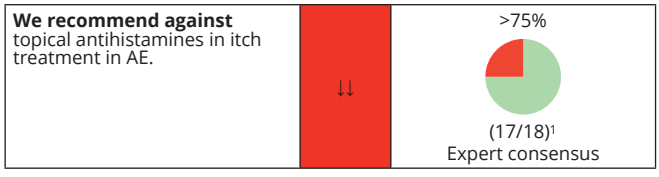
The systemic anti-inflammatory agent dupilumab showed high effectiveness in reducing itch in AE patients.[115-118] Similar data exist for other systemic drugs recently licensed for AE treatment, such as tralokinumab, abrocitinib, baricitinib and upadacitinib (see chapters biologics and JAK-Inhibitors).[119-122]

Antipruritic treatment

Polidocanol

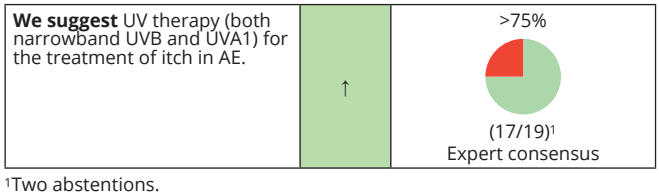


Topical antihistamines



1One abstention.

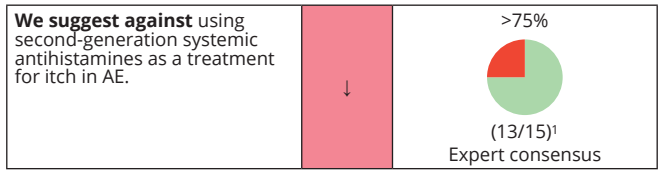
UV therapy



1Two abstentions.

UV phototherapy relieves pruritus in AE, which has been demonstrated in several studies. A systematic review of 19 RCTs suggests that narrowband UVB and UVA1 are the most effective forms of phototherapy in the treatment of AE, including reduction in itch intensity.[123] A recent study by Jaworek *et al*.[124] documented that narrowband UVB reduces itch in AE patients significantly better than ciclosporin.[124] There are no data specific to using UV phototherapy to treat itch in AE patients that would lead to recommendations that would differ from the general recommendations for using UV phototherapy in the treatment of AE.

Systemic antihistamines



1One abstention.

Antihistamines (AH) have been used for decades in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and the majority of them showed only a weak or no effect in decreasing pruritus.[125-133] A recent Cochrane review did not find consistent evidence that H1 AH treatments are effective as 'add-on' therapy for AE when compared with placebo.[134] The certainty of evidence for this comparison was of low to moderate quality.[134]

Especially, the first generation of systemic AH may affect sleep quality and reduce rapid eye movement (REM) sleep. Therefore, regular long-term use of sedating antihistamines is not recommended.[135-137]

Systemic antihistamines

Systemic antihistamines are not reimbursed by the SSN for AD in Italy. The reimbursement of these drugs is limited to the following non-AD condition: patients suffering from medium and severe allergic pathologies (seasonal allergic rhino-conjunctivitis, persistent non-vasculitic urticaria) that need prolonged treatment periods (over 60 days). These conditions must be certified by a SSN specialist (note 89). (https://www.aifa.gov.it/nota-89)

Selective serotonin reuptake inhibitors

We suggest against the use of selective serotonin reuptake inhibitors as a treatment for itch in AE patients.	↓	100% agreement  (20/20) Expert consensus

Phototherapy and photochemotherapy

We recommend narrowband UVB and medium-dose UVA1 for AE patients with moderate-to-severe AE.	↑↑	>95%  (24/25) Expert consensus
We suggest the use of narrowband UVB or UVA1 in children and adolescents after the assessment of skin type (see background text), but frequent and/or protracted treatment cycles should be avoided.	↑	>95%  (24/25) Expert consensus
We suggest that other phototherapy modalities (balneophototherapy, UVAB, BB-UVB, UVA) are to be considered as a second choice.	↑	100% agreement  (25/25) Expert consensus
We suggest that PUVA therapy is only used when previous treatment cycles with other phototherapies were ineffective or when approved drug treatments are contraindicated, ineffective, or have caused side effects.	↑	100% agreement  (25/25) Expert consensus
We suggest co-treatment with topical emollients during phototherapy.	↑	100% agreement  (25/25) Expert consensus
We recommend against the use of prolonged or repeated treatment cycles and maintenance regimens with all phototherapy modalities.	↓↓	100% agreement  (24/24) Expert consensus
We recommend against the use of all phototherapy modalities in patients with a history of skin cancer and with an increased risk of skin cancer (including photodamaged skin and those on systemic immunosuppressants — see background text)	↓↓	100% agreement  (25/25) Expert consensus

Efficacy of different photo(chemo)therapy modalities in clinical trials

Photo(chemo)therapy can be used in patients with moderate-to-severe AE recalcitrant to topical therapy. Background information on photobiology, UV modalities and practical aspects can be found in the full version of the guideline. Further information on the systematic review of Garritsen *et al*. is found in the full guideline version.[123] We must, however, emphasize that the use of phototherapy for AE is largely empiric and based on relatively few evidence-based data. There is a clear need for further research on the effectiveness and safety of phototherapy in AE, given that it is frequently used in AE patients.[138]

Safety of different photo(chemo)therapy modalities in clinical trials

It is evident that our current knowledge on the safety of phototherapy in patients with AE is poor because there are no data from RCTs or registries enrolling large patient cohorts and with prolonged follow-up.

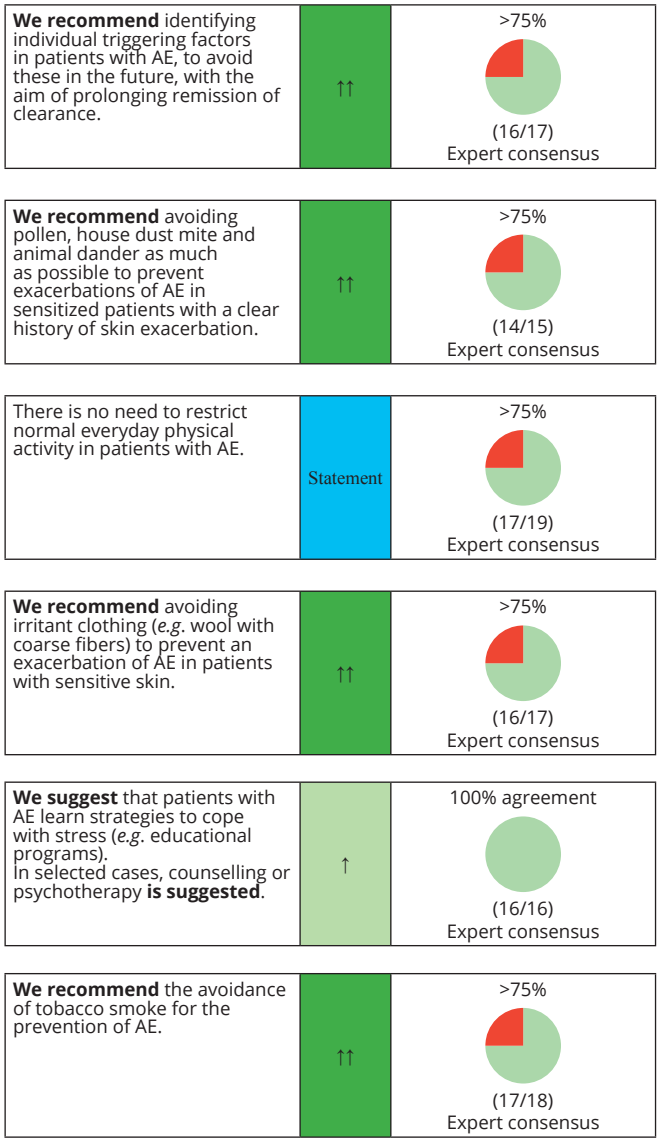
The cancerogenic risk of PUVA is well demonstrated in psoriatic patients, and therefore caution is also recommended in AE patients.[139-141] However, extrapolating the magnitude of the risk observed with PUVA in patients with psoriasis to the risk in patients with AE is not always correct because psoriatic patients (historically) may have been treated more often with immuno- suppressants and/or mutagenic drug therapies. In patients who use systemic immunosuppressants, especially ciclosporin and azathioprine, phototherapy is not recommended based on their risk of co-carcinogenicity (see chapter conventional systemic drugs).[142] There are few papers available on combination therapy and long-term safety in psoriatic patients;[143, 144] no papers were found specifically for AE (see the full version of the guideline).[1]

Phototherapies in Italy

NB-UVB phototherapy is available in many dermatology departments in Italy although the service opening hours vary from 1 hour every other day to 8 hours daily. UVA1 phototherapy is routinely available only in 3 Italian hospi-

tal centers. The use of PUVA photochemotherapy is limited to few hospital centers and psoralen tablets and solutions are no more available on the Italian pharmaceutical market (https://www.aifa.gov.it/farmaci-attualmente-carenti).
Patients must contribute to the cost of the treatment (a co-pay system called "ticket") and the fee charged to patients varies from 2 to 16 Euros per session with differences among Italian regions.
Only patients with Von Zumbusch's pustular psoriasis or psoriatic arthritis are exempt.

Avoidance techniques in atopic eczema



House dust mite avoidance

House dust mite (HDM)-related flares may occur in AE patients. Some house dust mite allergens identified by specific IgE or skin prick testing are enzymatically active compounds, which can destroy the cutaneous permeability barrier and may evoke the development of eczematic inflammation in sensitized atopic individuals.

The evidence on HDM avoidance techniques in prevention of atopic flares is somewhat controversial.[145-147] Measures to reduce exposure include mattress encasing, the use of adequate indoor ventilation (filter, well-aeration), and the avoidance of wall washing on high temperature.[39] HDM, a common indoor allergen occurring in dust, may be reduced by cleaning regularly. Complete eradication by encasing, for example, is not possible.

Animal dander avoidance

When allergies to furry animals are evident, their avoidance is recommended.[39] Exposure to cat allergens in particular may be a risk factor for developing inflammatory skin lesions and respiratory symptoms in sensitized patients with AE.[148] There may be an exception for dogs due to a suggested general protective effect of dog-keeping in the development of AE.[149]

Exercise/perspiration/physical activity

In AE patients, heat and excessive sweating are one of the main factors reported to exacerbate itch.[150] When excessive sweat is left on the skin, it can lead to occlusion of the sweat pores and formation of keratin plugs which in turn may cause local inflammation and itch. Some of the components of sweat include histamine, antimicrobial peptides and proteases which can induce itch. Sweat can also facilitate the penetration of allergens through the defective atopic skin barrier leading to mast cell degranulation.[151, 152] As sweat is important for skin homeostasis, it is not possible to avoid sweating completely. However, it should be washed off with consistent application of emollients as soon as possible to avoid inducing itch. The evidence concerning physical activity as a trigger for AE is conflicting and incomplete.[150] Although physical activity often leads to sweating, it is important for both physical and mental health, and AE patient should not be advised to avoid it.

Clothing

In patients with AE, certain fabrics such as wool can cause a tingling sensation, skin irritation and itch. The evidence is not completely clear on which fabrics to recommend

and which to avoid. Clothing-related exacerbation can be subjective.[153] There is no evidence from high-quality studies that certain fabrics decrease the severity of AE.[153, 154] In general, textiles with course fibers, such as certain wool garments and occlusive clothing leading to overheating, should be avoided. Otherwise, the choices of clothing should be based on individual preferences. Most AE patients tolerate silk and cotton well, whereas contact with wool is frequently irritating.

Psychological stress

There is good evidence that AE is associated with depression, anxiety and reduced QoL.[155, 156] It is difficult to investigate whether the psychological stress is a cause or consequence of the AE exacerbation, and in many cases, it is probably both. There is a positive correlation between maternal stress and offspring AE.[157, 158] Although evidence from larger studies is lacking, patients report that stress induces itch and flaring of the disease[159, 160] (see chapter psychological intervention).

Psychological and psychiatric assistance for patients with atopic dermatitis in Italy

Healthcare for patients with a psychiatric disease is free in Italy. A nation-wide network of Departments of Mental Health delivers outpatient and inpatient care, but also run semi-residential and residential facilities. Hospital care is delivered through small psychiatric units. There are also many private inpatient facilities operating in Italy.
AD patients with a symptomatic psychological distress may be referred by dermatologists to outpatient psychological or psychiatric structures for drug treatment and counselling. Officially structured multi-disciplinary dermatologist-psychiatric or dermatologist-psychologist facility is available only in a very limited number of hospitals.

Tobacco smoke

The association of AE with active smoking was found to be significant in a meta-analysis (OR=1.87, 95% CI: 1.32-2.63). This association remained significant when looking at only children, only adults and by geographic region. Moreover, the effect of exposure to passive smoke on AE flares is small but also significant (OR=1.18, 95% CI: 1.01-1.38). Passive smoke was associated with the prevalence and severity of AE both in children and in adults.[161] The results of a recent registry study of 908 patients with atopic eczema suggest that the intensity of lesions and the Patient Global Assessment Score (PGA) were higher in smoking patients (N.=352) than in non-smoking patients (N.=556). However, physician-assessed disease severity (oSCORAD and EASI scores) did not differ between smokers and non-smokers in this study.[162]

Dietary interventions in atopic eczema

We recommend identifying individual triggering factors in patients with AE, to avoid these in the future, with the aim of prolonging remission of clearance.	↑↑	>75%  (16/17) Expert consensus
IgE-mediated food allergy (immediate reactions) **We recommend** avoiding pollen, house dust mite and animal dander as much as possible to prevent exacerbations of AE in sensitized patients with a clear history of skin exacerbation.	↑↑	
IgE-mediated food allergy (immediate reactions) plus food-induced AE "delayed hypersensitivity": **We recommend** diagnostic procedures for the elucidation of combined reactions to foods (immediate reactions plus food-induced eczema [food-specific IgE and/or PST, diagnostic elimination diets and challenge test]) in AE patients with a history of *food-induced symptoms, including worsening of AE*.	↑↑	>75%  (16/18)[1] Expert consensus
History or suspicion of food-triggered AE "delayed hypersensitivity": **We suggest** diagnostic procedures for the elucidation of food as a trigger factor of AE (food-specific IgE and/orSPT, diagnostic elimination diets and challenge tests) in patients with moderate-to-severe AE and with a history or suspicion of *food-triggered AE*.	↑	

[1]One abstention.

A therapeutic elimination diet **is recommended** after the individual diagnosis of food allergy or food-induced eczema in AE.	↑↑	100% agreement  (17/17) Expert consensus
We recommend the re-evaluation of a child's IgE-mediated food allergy after one or two years after strict elimination diet.	↑↑	100% agreement  (17/17) Expert consensussus

We recommend against general dietary interventions (*e.g.* other supplements, general avoidance of certain foods e.g. cow's milk, gluten) for the management of AE.	↓↓	100% agreement (19/19) Expert consensus
We cannot make a recommendation on probiotics for the management of AE.	0	100% agreement (19/19) Expert consensus
We recommend against vitamins as a treatment for AE.	↓↓	100% agreement (17/17) Expert consensus

Food allergens, pre- and probiotics

Food allergy has been documented in approximately one-third of children with moderate–to-severe AE.[163, 164] Among food allergens, cow's milk, hen's egg, peanut, soya, nuts and fish are most frequently responsible for immediate-type food allergy and AE exacerbation in young children, with age-dependent variations in causally incriminated food.[165] In older children, adolescents and adults pollen-associated food allergy should also be taken into account.[166-168]

For further details on response patterns to food allergens, see the full version of the guideline.

Pre- and probiotics and dietary supplements

Probiotics such as lactobacillus mixtures have been studied in AE and have been shown to induce improvement in some settings.[169] Other studies failed to show significant effects.[170, 171] In a study with 800 infants, the effect of a prebiotic mixture was investigated and found to have beneficial effects in preventing the development of AE.[172] A recent Cochrane review identified 39 randomized controlled trials involving 2599 randomized participants.[173] The authors concluded that compared with no probiotic, currently available probiotic strains probably make little or no difference in improving patient-rated eczema symptoms. However, in 2020, the systematic review by Tan-Lim *et al.* found that certain probiotic preparations (*Bifidobacterium animalis subsp lactis* CECT 8145, *Bifidobacterium longum* CECT 7347, and *Lactobacillus casei* CECT 9104; *Lactobacillus casei* DN-114001) show benefit in reducing allergic symptoms in pediatric AE.[174]

A systemic review on dietary supplements including fish oil, vitamin D or vitamin E came to the conclusion that there is no convincing evidence of the benefit of dietary supplements in AE.[175]

Allergen specific immunotherapy

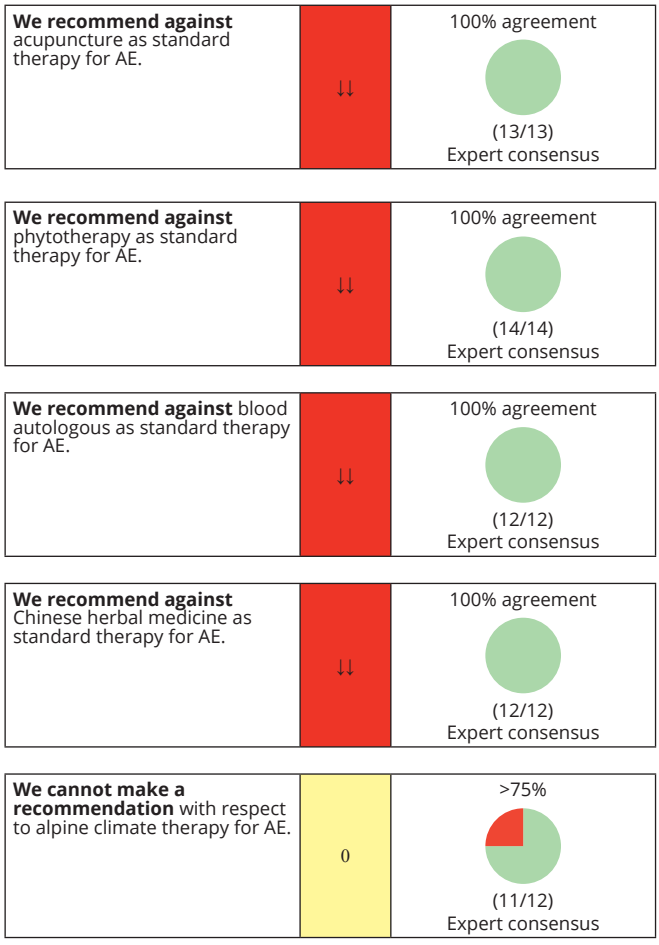
We recommend against allergen-specific immunotherapy as a routine treatment option for AE.	↓↓	>50% (8/13) Expert consensus
We suggest that AIT is considered for selected patients with aeroallergen sensitization and a history of clinical exacerbation after exposure to the causative allergen.	↑	100% agreement (11/11) Expert consensus

The cause of symptoms in allergic patients is that the sensitized individual reacts with an allergic immune response to an otherwise harmless allergen. The aim of allergen-specific immunotherapy (AIT) is to theoretically cure allergic diseases. The role of allergen sensitization in AE pathogenesis has been investigated but remains to be fully elucidated. Inflammatory processes seem to be mediated by both an immediate-type reaction, initiated by the internalization of the complex IgE specific/allergens from epidermal dendritic cells, and a delayed T-cell reactivity, characterized by a Th2 inflammatory pattern.[135]

One of the most important allergen sources in AE are HDM due to the perennial exposure. Recent studies have also focused on the role of pollen allergens as a trigger for AE flare-ups.

AIT consists of administering increasing doses of allergen to modulate the response and promote peripheral immune tolerance mechanisms. AIT induces a shift from a Th2 to a Th1 immune response pattern, a decrease of mediator release from mast cells and the production of blocking antibodies IgG4.

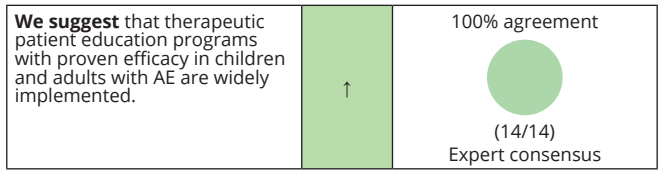
Complementary medicine



Complementary medicine describes a wide variety of healthcare practices used alongside standard medical treatment. These include alternative health approaches such as traditional Chinese medicine, acupuncture, autologous blood therapy, phytotherapy and high-altitude alpine climate. Overall, the evidence to support any of these treatments for AE was not strong enough. Further details on our critical appraisal are found in the full version of the guideline.

In Italy, complementary medicine is never reimbursed by the SSN and it must be paid out of the pocket by patients to private physicians.

Psychological and educational interventions



Psychological and emotional factors as well as psychodynamic structures within the family are well-known elements that may influence the clinical course of AE.[176] Stress can elicit severe exacerbations of the disease and perpetuate the itch-scratch cycle. Anxiety or depression are acknowledged comorbidities in AE patients.[156] Furthermore, poor QoL and adherence to treatment are key issues in these patients.[177] As a multidimensional phenomenon, low treatment adherence is influenced by factors such as the disease itself, its chronicity but also by the patient's beliefs and characteristics. It can be improved by introducing specific strategies after understanding the patient's adherence pattern.[177] Therapeutic patient education (TPE) programs were originally designed to enable people with chronic diseases to manage their illness (increasing autonomy and decreasing medical complications). They can help patients and their families to better understand and accept their disease and cope with treatment in order to improve QoL and treatment adherence. The aim of TPE is not simply to provide information by leaflets, but entails the transfer of skills (*e.g.* disease self-management strategies, knowledge of treatments, relaxation and behavioral therapy techniques) from a trained healthcare professional to the patient or their parents.[178] Additionally, as TPE is patient-centered holistic care, it should facilitate a better partnership between doctors and their patients/caregivers. TPE can also help restore family dynamics. Parents with negative treatment experiences in the past and poor coping abilities regarding scratch control are likely to benefit most from TPE programmes.[179]

High-quality TPE programs should ideally be evidence-based, tailored to a patient's needs, taking into account the individual educational and cultural background (rather than being standardized in form and content). It should also have well-defined content and activities that are provided by an interdisciplinary healthcare team.[180]

There is also some evidence for nurse- and psychologist-led programs as well as e-health education. For further details see the full version of the guideline.

Structured interdisciplinary high-quality education programs should be implemented regardless of the severity of AE. They can improve the efficacy of topical treatment

and be particularly helpful in evaluating the next treatment steps, like the necessity of introducing systemic treatments. Psychological interventions, for example autogenic training, relaxation, cognitive-behavioral therapy, habit reversal and behavioral therapies have a positive effect on different aspects of AE.

Pregnancy, breastfeeding and family planning

The current ethical framework of GCP guidelines deems it unethical to perform clinical trials in pregnant women. Therefore, there is no high-level evidence on efficacy and safety in this patient population. AE is the most common general skin disease in pregnancy. AE may either: 1) worsen in women with a chronic condition; or 2) may be reactivated in patients with a past AE history; or 3) may occur in women with no AE history (atopic eruption of pregnancy, AEP). Worsening of AE is mostly reported during the second and third trimesters, while AEP typically occurs during the first trimester.[90] There are no major clinical differences between classical AE worsening and AEP. Physiological skewness of the immune system towards a Th2-dominated response during pregnancy as well as physical and psychological stress during this period may contribute to AE worsening during pregnancy. Little is known about treatment patterns during pregnancy, but patients and caregivers tend to reduce the use of topical and systemic therapies to avoid presumed harm to the fetus.[181] Consequently, undertreatment of AE during pregnancy may lead to serious QoL impairment but also to complications such as eczema herpeticum or *Staphylococcus aureus* skin infections, and should therefore be avoided.

Pregnant women

In pregnant women with AE, **we recommend against** long-term use of systemic corticosteroids — as we do in all AE patients.	↓↓	100% agreement (16/16) Expert consensus
In pregnant women with AE, **we suggest** prednisolone only as short-term rescue therapy for acute flares.	↑	

In pregnant women with AE, **we recommend against** the use of abrocitinib, baricitinib, upadacitinib, methotrexate, and mycophenolate.	↓↓	100% agreement (12/12) Expert consensus

In pregnant women with AE, **we cannot make a recommendation** regarding the use of dupilumab during pregnancy due to the lack of clinical data.	0	100% agreement (16/16) Expert consensus
In pregnant women with AE who are candidate for systemic treatment, **we suggest** ciclosporin.	↑	100% agreement (14/14) Expert consensus
In pregnant women with AE who are being treated with azathioprine, and still need a systemic treatment, **we suggest** continuing azathioprine.	↑	100% agreement (14/14) Expert consensus
In pregnant women with AE, **we recommend** TCS class II or III.	↑↑	100% agreement (19/19) Expert consensus
In pregnant women with AE, **we suggest** that TCI may preferably be used on the face and intertriginous areas an on abdominal, breast and thigh skin, where the striae formation increases with excessive use of TCS.	↑	100% agreement (19/19) Expert consensus
In pregnant women with AE, when topical treatments are insufficient, **we recommend** narrowband UVB (311 nm) or broad-spectrum UVB therapy if NB-UVB is unavailable.	↑	100% agreement (19/19) Expert consensus

First-line treatments

Emollients

Basic emollient therapy is key in the treatment of AE also during pregnancy and must be proposed to pregnant women with AE as a basic daily therapy. There is no firm evidence on which emollient should be used, but using one with a high lipid content and as few potentially harmful agents as possible is recommended. Using emollients in a wet wrap technique is encouraged.[5]

TCS

Reactive or proactive use of TCS class II or III is recommended. A Cochrane systematic review updated in 2015

including 14 studies (five cohort and nine case-control studies) with 1.601.515 study subjects has examined the risk of TCS use in pregnancy. Overall, it has been deemed safe, with no causal associations between maternal exposure to TCS of all potencies and pregnancy outcomes including mode of delivery, congenital abnormalities, preterm delivery, fetal death, and low Apgar score, although the use of very potent topical corticosteroids may be associated with low birthweight.[182] Proactive, twice weekly TCS application as maintenance therapy is regarded as safe, but caution is recommended when using potent TCS over large body surface areas, or sensitive areas such as breast and thigh skin, on a more regular basis. Some experts suggest that class IV may be used as rescue therapy, or over longer periods on limited skin areas, but this is controversial. Fluticasone propionate should be avoided as it is the only TCS that is known not to be metabolized by the placenta.[90]

TCI

Reactive and proactive use of TCI may be preferable on the face and intertriginous areas, and on abdominal, breast and thigh skin, where the risk of striae formation increases with excessive use of TCS.

Antiseptics

Antiseptics, except triclosan, may be used by pregnant women if clinically needed to prevent recurring skin infections, but are not recommended as a general routine measure.

UV phototherapy

Therapy with narrowband UVB (311 nm) and broad-spectrum UVB does not impose a risk to the fetus in pregnant woman. However, oral psoralen should not be used preconceptionally (3 months) or in pregnant women.

Second- and third-line treatments

Second- and third-line treatments are recommended in pregnant women with AE who are inadequately controlled with TCS class II or III.

Systemic corticosteroids should not be used in the long-term in AE in general and even more so not during pregnancy, as it is associated with an increased risk of fetal complications, including gestational diabetes.[182] Only short courses of prednisolone (maximum 0.5 mg/kg/d) may be used with strict indication.

Ciclosporin may be used off-label in severe uncontrolled AE during pregnancy if topical anti-inflammatory treatment alone or in combination with UV treatment failures, and there is a clear need for better long-term disease control. However, extra attention should be given to the renal function and blood pressure of the mother. There is no evidence of teratogenicity. Ciclosporin crosses the placenta[183] and should not be used during pregnancy, unless the potential benefit to the mother justifies the potential risk to the fetus.

AZA may be used off-label in pregnant women with severe uncontrolled AE who are already receiving this treatment at the time of conception. There is no evidence for teratogenicity from studies with patients with inflammatory bowel diseases. Closely consulting an experienced obstetrician when prescribing this drug is strongly recommended.[90]

MTX and mycophenolate mofetil are teratogenic and therefore strictly contraindicated during pregnancy.

We cannot recommend any of the novel systemic medications, as there are currently no clinical data available to inform about any potential drug-associated risks. Pre-clinical data do not indicate that there would be a teratogenic potential of dupilumab or tralokinumab if given during pregnancy.

Abrocitinib, baricitinib and upadacitinib are contraindicated during pregnancy according to label. There are no clinical data but single case reports supporting its safety in pregnant women, but teratogenic effects have been described in animal models.

Antihistamines are of limited efficacy in AE (see chapter anti-pruritic treatment). In case of need, loratadine should preferentially be used because of the broad experience with this drug in pregnant women.

Due to lack of experience with crisaborole during pregnancy, this drug should not be used preconceptionally, in pregnancy or during lactation.

Specific consideration for breastfeeding women

In breastfeeding women with AE, **we recommend** TCS class II or III.	↑↑	>75%  (16/17) Expert consensus
In breastfeeding women with AE, **we suggest** prednisolone only as short-term rescue therapy for acute flares.	↑	
In breastfeeding women with AE, **we suggest against** methotrexate, abrocitinib, baricitinib, upadacitinib, azathioprine, and ciclosporin.	↓	
In breastfeeding women with AE, **we cannot make a recommendation** regarding the use of dupilumab due to the current lack of clinical data.	0	

TCS and TCI: No studies have examined the safety of TCS and TCI use during lactation but no harmful effect is suspected. Nevertheless, it is recommended to apply the topical treatment in the nipple region immediately after nursing the child, to allow the drug to be absorbed into the skin before the next feeding.[90]

Systemic corticosteroids: Treatment with a short course of a systemic corticosteroids during lactation is safe, since <0.1% of the mother's ingested dosage is secreted into breastmilk.

MTX, AZA, ciclosporin and JAK inhibitors are secreted in breastmilk and may induce immunosuppression in the neonate. MTX, AZA, ciclosporin and JAK inhibitors are generally not recommended for lactating mothers.[90]

Family planning

In patients with AE planning to have a child, **we recommend** TCS II or III or TCI.	↑↑	100% agreement (22/22) Expert consensus
In women with AE planning to have a child, **we recommend** stopping methotrexate at least 3 months before conception.*	↑↑	>75% (13/14) Expert consensus
In men with AE planning to have a child, **we recommend** stopping methotrexate 3 months before conception.*	↑↑	

*EMA recommends 6 months as a means of precaution, the practice of the guideline group differs from this.

Preconception recommendations for women

TCS and TCI

Although the literature on this subject is very sparse, topical AE therapies in women wishing to conceive can be used without concern.

MTX

Local labels in different countries suggest a contraindication range spanning from 1 month to 6 months before conception. The European Medicines Agency (EMA) recommends 6 months as a means of precaution. The practice of the guideline group differs from this, and we recommend stopping methotrexate 3 months before conception.

Preconception recommendations for men

TCS and TCI: Although the literature on this subject is very sparse, topical AE therapies in men wishing to father a child can be used without concern.

Ciclosporin may be used in the treatment of AE in men at the time of conception, as there is no evidence for harm or decreased fertility.

MTX: Following the European S3-guideline on systemic treatment of psoriasis vulgaris, a 3-month MTX pause prior to conception is recommended. However, (inadvertent) exposure beyond this time does not justify termination of pregnancy, because there is no evidence of male teratogenicity.[90]

AZA and baricitinib: there is no contraindication for the use of AZA and baricitinib in men wishing to father a child.

Considerations for pediatric and adolescent patients

AE may appear during the first months of life, and most patients develop the condition before the age of 5 years. Around 60% of children outgrow AE in some cases. However, significant numbers present with either AE or hand eczema as adults.[184]

Severe early disease and a family history of AE may predict a more persistent course.[15]

During infancy (0-2 years), the predeliction areas are the cheeks, head, trunk, and extensor surfaces of the extremities, although flexural involvement is also common, which becomes an even more prominent feature during later childhood.

The first clinical signs often appear on the cheeks in form of erythematous, oozing, crusted plaques. The symptoms may then generalize and spread to the scalp, forehead, trunk and limbs. Centrofacial pallor along with spared area of the nose and paranasal skin cause the 'headlight sign' appearance. The diaper area is also usually intact in infancy. The facial symptoms usually decrease by the end of the first year.[185]

Prematurity causes barrier dysfunction with higher transepidermal water loss (TEWL) and increased percutaneous absorption of chemicals. This is an important factor when planning local treatment dosage, body area, and duration. Infants are more susceptible to percutaneous toxicity. Their high surface area-to-volume ratio, immature drug metabolism systems, and decreased subcutaneous fat stores increase the absorption potential of the skin, while decreasing the volume of distribution of a drug or toxin. In full-term infants, skin barrier development continues during the first year of life.

Bathing an infant provides important psychological benefits between parent and child. Bathing of infants with AE should be brief to maintain the microbial flora, which

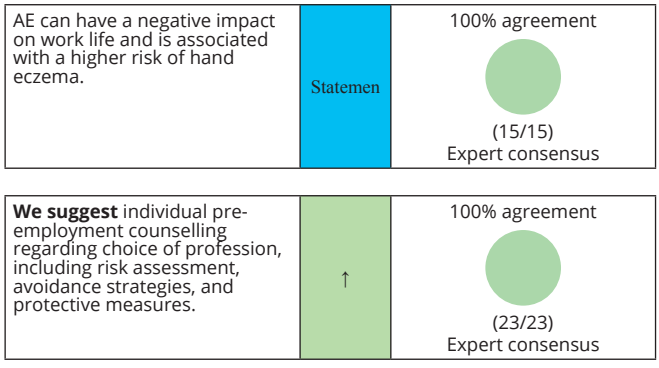
changes with age, avoiding harsh soaps and detergents and using bath emollients to aid skin hydration and emollients as soap substitutes to aid barrier function.[186]

Wet wraps can be a useful treatment approach where additional hydration of the skin is needed, in particular in young children.[46]

With mild disease activity, maintenance use of topical corticosteroid twice to three times weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60-90 g in adolescents and adults, adapted to affected body surface area) with a liberal use of emollients do not result in adverse systemic or local effects.[15]

To treat the face of a 3-month-old infant, one FTU will suffice. To fully cover an entire leg of a 6-year-old, a 4 FTU dose is used. TCI may effectively and safely be used as anti-inflammatory agents in the treatment of AE, especially on sensitive skin areas (*e.g.* face), from age two. The use of TCI in younger children is common.[135] Daily application (BID) is recommended during relapses on the affected area, following the FTU rules, while according to the proactive regimen they may also be applied twice a week on the symptom-free areas.[15] TCI are also used under 2 years of age in many centers.

Occupational aspects



A number of occupational aspects are relevant to AE patients, as they run a significant risk of developing occupational contact dermatitis. Atopy amplifies the effects of irritant and allergen exposure in several professions such as hairdressers, nurses, metal-workers, mechanics and cleaners, where hand eczema is a very common disease.[135] The risk of hand eczema in AE patients is increased about fourfold.[187] Physicians should inform AE patients about the increased risk, and provide good guidance about prophylactic skin protection and irritant/contact allergen avoidance. All dermatologists treating adolescent patients with AE should advise these early on occupational aspects of their skin disease and suitable career choices.[135] For further information on impact of AE on work life, see Table III and the full version of the guideline.[1]

Procedure for recognition of civil disability and invalidity for psoriasis in Italy

Patients suffering from a severe form of psoriasis can apply for civil invalidity and disability due to chronic disease by submitting electronically the application with the medical documentation certifying the illness and the degree of severity to the Italian national social security institute (Istituto Nazionale Previdenza Sociale, INPS).

Strengths and limitations

The vision of this guideline was to provide a comprehensive evidence-based update on all aspects of AE care with high relevance to practising clinicians across Europe. To reflect the latest methodological rigour in guideline development, the formal structure of the guideline document has been changed to follow the structure and style of the EuroGuiDerm guidelines.[1] We assembled a guideline development group (GDG) that included clinical and methodological experts from across Europe, including patients. Our clear conflict of interest policy has created more transparency and was also reflected in the online voting procedures on standardized guideline statements.

While this regulated process of guideline formation has resulted in higher methodolocal rigour, independence, objectivity and quality of the content, we are conscious that the guide- line document is already outdated regarding the fastest changing content, in particular the chapter on systemic therapy. However, we plan to update the content of this aspect of the guideline on a regular basis, creating a 'living' guideline for systemic AE therapies.

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TABLE III.—*Occupations with an elevated risk of hand eczema.*

Job/occupation	Possible sensitizing compounds and atopic eczema triggers
Hairdresser	Hair dyes, perm products, haircare products, rubber auxiliary materials, bleaching agents, detergents, wet-work, cosmetic preservatives
Beautician	Acrylics, acrylates, cosmetic preservatives, rubber auxiliary materials, wet-work
Cleaning and housekeeping	Disinfectants, rubber auxiliary materials, abrasives, wet-work
Baker	Flour and grain dust, rubber auxiliary materials, wet-work
Painter	Paints, isocyanates, resins, turpentine, paint pigments, preservatives
Construction and cement worker	Isocyanates, cement, concrete, glues, paints, resins, fiberglass, metals
Carpenter	Wood
Agricultural worker	Animal particles, disinfectants, plants, rubber auxiliary materials
Florist and gardener	Plants, rubbery auxiliary materials, wet-work
Healthcare worker	Latex, disinfectants, rubbery auxiliary materials, medications, wet-work
Veterinarian, animal lab worker, zookeeper	Animal particles, disinfectants, rubber auxiliary materials, medications, tools, wet-work
Catering and cooking employees	Detergents, disinfectants, foods, rubber auxiliary materials, wet-work
Wind energy technician	Solvents, glues, paints, epoxy, resins, fiberglass, acids and alkalis, detergents
Mechanic and metal worker	Cutting fluids, coolants, detergents, metals, petroleum products, preservatives

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Conflicts of interest (authors of the Italian Adaption of the Euroguiderm Guidelines)
Grants or contracts: Francesco Cusano (Jannsen, Leo Pharma, Novartis, Sanofi), Luigi Naldi (Galderma, Sanofi). Consulting fees: Paolo Amerio (Sanofi); Luigi Naldi (BMS, Galderma, Sanofi), Cataldo Patruno (Sanofi), Paolo D. M. Pigatto (Abbvie, Leo Pharma, Sanofi), Andrea Chiricozzi (AbbVie, Almirall, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi). Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Monica Corazza (Abbvie, Almirall, Jannsen, Leo Pharma, Lilly, Novartis, Sanofi), Paolo Amerio (Abbvie, Galderma, Jannsen, Novartis, Pfizer, Sanofi), Luigi Naldi (Galderma), Cataldo Patruno (Abbvie, Leo Pharma, Lilly, Sanofi), Paolo D. M. Pigatto (Abbvie, Sanofi, Leo Pharma), Andrea Chiricozzi (AbbVie, Almirall, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi), Luca Stingeni (Abbvie, Amgen, Leo Pharma, Lilly, Novartis, Pfizer, Sanofi). Support for attending meetings and/or travel: Monica Corazza (Abbvie, Almirall, Jannsen, Leo Pharma, Lilly, Novartis, Sanofi); Paolo Amerio (Abbvie, Novartis, Sanofi), Luigi Naldi (Sanofi); Paolo D. M. Pigatto (Leo Pharma, Sanofi), Francesco Tonon (Abbvie, Sanofi, Leo Pharma). Participation on a Data Safety Monitoring Board or Advisory Board: Luigi Naldi (Abbvie, Sanofi), Paolo D. M. Pigatto (Sanofi), Luca Stingeni (Abbvie, Leo Pharma, Sanofi).

Conflicts of interest (original authors)
Sebastien Barbarot received personal fees from Bioderma, Laboratoire La Roche Posay, SanofiGenzyme, AbbVie, Novartis, Janssen, Leo-Pharma, Pfizer, Lilly, UCB, FreseniusKabi, Samsung bioepis, Biogen; Thomas Bieber is/has been lecturer and/or consultant for following companies: AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, BioVerSys, Böhringer-Ingelheim, Daichi-Sankyo, Davos Biosciences, Dermavant/Roivant, DS Pharma, Evaxion, FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incytes, Kymab, LEO, Lilly, L'Oréal, MenloTx, Novartis, Pfizer, Pierre Fabre, Sanofi/Regeneron, UCB; Mette Deleuran declared the participation in advisory boards and/or the activity of speaker for Sanofi-Genzyme, Regeneron, Galapagos, Eli-Lilly, Pfizer, Leo-Pharma, Pierre Fabre Dermocosmetique, Almirall, and AbbVie; Giampiero Girolomoni recieved personal fees for attending advisory boards or as a speaker at sponsored meetings from Sanofi, Regeneron, Galderma, Almirall, Abbvie, Pfizer, Leo pharma, Novartis, Eli Lilly; Uffe Nygaard received honorary from Sanofi Genzyme A/S for teaching and providing written patient information regarding AE; Johannes Ring received honoraria for lectures from Abbvie and Allergika; Rehbinder Eva Maria received honoraries for lectures from Sanofi Genzyme, Leo Pharma, Novartis, Norwegian Psoriasis and Eczema Association, Norwegian Asthma and Allergy Association; Serra-Baldrich Esther received honorary as speaker, consultant, boards, for Pfizer, Sanofi, Novartis, Lilly, Abbvie, Galderma, Leo; Jacek C. Szepietowski is/has been an Advisory Board Member of Leo Pharma, a speaker for Leo Pharma and SanofiGenzyme and an investigator for Regeneron, Pfizer; Antonio Torrelo received honoraries from Lilly, Sanofi, Pierre Fabre, Pfizer, Abbvie (all advisory boards and/or lectures and/or clinical trials); Thomas Werfel declared advisor and research funding from companies currently active in AE, research: Sanofi, Lilly, Pfizer, LEO, Galderma; Andreas Wollenberg declared honoraries from AbbVie, Lilly, Pierre Fabre, Sanofi, Galderma, L'Oreal, Leo, Novartis.

Authors' contributions
All authors read and approved the final version of the manuscript.

History
Article first published online: May 10, 2024. - Manuscript accepted: March 29, 2024. - Manuscript received: March 27, 2023.